IFW 1654

I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail, in an envelope addressed to: MS Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Dated: October 25, 2005 Signature: Greta E. Noland (Greta E. Noland)

*

+Docket No.: 11009/35975C (PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Olaf B. Kinstler et al.

Application No.: 09/817,725 Confirmation No.: 1724

Filed: March 26, 2001 Art Unit: 1654

For: N-TERMINALLY CHEMICALLY MODIFIED PROTEIN COMPOSITIONS AND METHODS Examiner: B. D. Chism

FOURTH INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. §1.97(c)

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicants request that the documents listed on the attached Form 1449 be made of record in the above-identified patent application. Copies of each of the listed documents which are foreign patent applications/patents or journal articles/abstracts are attached. This information disclosure statement is not an admission that a search has been made, that other relevant art does not exist, or that any of the information disclosed herein constitutes prior art under 35 U.S.C. §102 or §103.

This information disclosure statement is submitted before the mailing date of a final action or notice of allowance and is accompanied by our check in the amount of the fee of $180.00 set forth in 37 C.F.R. §1.17(p) as is required for the information disclosure statement to be considered under 37 C.F.R. §1.97(c). The Commissioner is hereby authorized to charge any fees except the issue fee which may be required, or any credit any overpayment, to Deposit Account Number 13-2855. A duplicate copy of this sheet is enclosed.

10/28/2005 HLE333 00000028 09817725
04 FC:1806 180.00 OP

I. Resubmission of Documents

The 1449 form for this fourth information disclosure statement (IDS) re-lists Documents B31-B40, C24 and C26 which were originally included on the second IDS submitted in the present application, the IDS dated June 19, 2002. The outstanding Office Action states that these documents were not considered by the examiner either because no English language translation was provided (B31-B40) or because a copy was not attached (C24 and C26).

The 1449 form submitted herewith indicates that B31 is a Japanese language equivalent of B20 that was previously considered by the examiner, B35 is a Japanese language equivalent of B23 that was previously considered by the examiner, B36 is a Japanese language equivalent of B49 submitted herewith, and B37 is a Japanese language equivalent of A32 submitted herewith. English language translations of B32-B34 and B38-B40 are submitted herewith. Copies of C24 and C26 are also submitted herewith. The examiner is respectfully requested to consider documents B31-B41, C24 and C26 as well as the new documents listed on the fourth 1449 form.

II. Concise Explanations of Relevance of New Documents

A35 Clark, US 5,597,797
A37 Attie et al., US 5,646,113
A38 Clark et al., US 5,661,122
A40 Bunting et al., US 5,935,924
C63 Delgado et al., "Quantitative Analysis of Polyethylene Glycol (PEG) in PEG-Modified Proteins/Cytokines by Aqueous Two-Phase Systems"
C81 Lu and Felix, "PEGylated Peptides II Solid-Phase Synthesis of Amino-, Carboxy- and Side-Chain PEGylated Peptides"
C92 Truitt et al., "Pharmacodynamic and Preliminary Pharmacokinetic Evaluation of Pegylated Derivatives of Interferon-α2a"
C94 Watson et al., "Matrix-Assisted Laser Desorption Mass Spectrometric Analysis of a Pegylated Recombinant Protein"
C95 Yamasaki et al., "Modification of Recombinant Human Granulocyte Colony-Stimulating Factor (rhG-CSF) and Its Derivative ND 28 with Polyethylene Glycol"

A declaration under 37 C.F.R. §1.131 to antedate these documents is submitted herewith.

B56 Capon et al., WO 90/05534
B58 Carlsson et al., WO 93/00109

These two published applications describe pegylated CD4 (B56) and growth hormone (B58), respectively. The experiments at page 9, lines 13-35 of B56 and at

page 19, lines 5-14 of B58 were repeated. Copies of memos describing the analysis of products of the experiments are attached at the end of the copies of the two applications submitted herewith.

C66 Francis et al., "PEG-cytokines: Improved Pharmaceutical Properties and Dissociation of Individual Bioactivities"

C76 Knusli et al., "Polyethylene Glycol (PEG) Modification of Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) Enhances Neutrophil Priming Activity But Not Colony Stimulating Activity"

C82 Malik et al., "Polyethylene Glycol (PEG)-Modified Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) with Conserved Biological Activity"

These documents appear to describe a body of work by a research group involving coupling of MPEG to proteins and to GM-CSF specifically. The articles indicate that, when fractionated, a preparation of PEG-GM-CSF showed peaks corresponding to PEG_1-GM-CSF and PEG_2-GM-CSF and shoulder to PEG_3-GM-CSF, respectively.

B50 Shadle et al. EP 402 378 B

This application describes chemical modification of colony stimulating factor-1 with polymers to increase its circulating half-life. It states the protein is conjugated to the polymer via free amino groups, preferably only one or two in order to minimize loss of biological activity. It later states the residues to be conjugated may be ε-amino groups or a free amine group at the N-terminus.

C55 Acharya et al., "Schiff Base Adducts of Glyceraldehyde with Hemoglobin: Differences in the Amadori Rearrangement at the α-Amino Groups"

C64 DiDonato et al., "Selective Carboxymethylation of the α-Amino Groups of Hemoglobin: Effect on Functional Properties"

C56 Acharya et al., "Reductive Hydroxyethylation of Hemoglobin A: Functional Properties of Hemoglobin A Selectively Hydroxythylated or Dihydroxypropylated at the α-Amino Groups"

C57 Acharya et al., "Selectivity in the Modification of the α-Amino Groups of Hemoglobin on Reductive Alkylation with Aliphatic Carbonyl Compounds: Influence of Derivatation on the Polymerization of Hemoglobin S"

These publications appear to describe a body of work by a research group involving coupling of α-hydroxyaldehyde to hemoglobin. The group obtained preparations of hemoglobin that contained, among more highly modified species, a hemoglobin species modified only at the N-terminus. In the C64, the authors state "we demonstrate, through proper choice of pH and ratios of reactants, preferential reductive alkylation of the NH_2-terminal residues of the hemoglobin chain is possible."

B51 Nakano, EP 426 488 B

This patent discloses superoxide dimutases modified via their amine functional groups with residues of a polyoxyalkylene polymer such as polyethylene glycol..

A39 Hakimi et al. US 5,747,646
B52 Hakimi et al. EP 510 356 A1

The patent and related application describe polyethylene glycol protein conjugates. They state in a preferred embodiment one polyethylene glycol unit is conjugated to the protein and that such a conjugate can be obtained even when there are two or more free amino groups. They go on to state the activated PEG compound will react first with one of the free amino groups and that by regulating the concentration of the reagents such as the protein and reaction conditions, one can regulate the degree of pegylation of the free amino groups contained within the protein.

A41 Offord et al. US 6,673,347

This patent describes polypeptide and protein derivatives and processes for preparation of the derivatives. The polypeptides or proteins may be derivatized with a polymeric compound. The polymeric compound may be attached to the amino terminus of the polypeptide or protein.

A31 Bayer et al., US 3,772,264
B48 Obermeier et al., DE 2930542
C62 Das et al., "New Model Visual Pigments, Spectroscopy of Poly(ethylene glycol) Peptide Schiff Bases of Retinal"
C65 Ehrat and Luisi, "Synthesis and Spectroscopic Characterization of Insulin Derivatives Containing One or Two Poly(ethylene oxide) Chains at Specific Positions"
C80 Lu and Felix, "Pegylated Peptides I: Solid-Phase Synthesis of N^{α}-Pegylated Peptides Using Fmoc Strategy"
C84 Neubauer et al., "Influence of Polyethylene Glycol Insulin on Lipid Tissues of Experimental Animals"

These describe peptides or proteins that are PEGylated through the α-amino group at their N-terminus, while reactive ε-amino groups had been protected to prevent PEG attachment at those ε-amino groups.

C78 Kunitani et al., "On-Line Characterization of Polyethylene Glycol-Modified Proteins"

This article describes preparations of PEG—IL-2 that when subject to chromatography include 1.0 PEG.

C71 Katre et al., "Chemical Modification of Recombinant Interleukin 2 by Polyethylene Glycol Increases Its Potency in the Murine Meth A Sarcoma Model"
C72 Katre, "Immunogenicity of Recombinant IL-2 Modified by Covalent Attachment of Polyethylene Glycol"
C75 Knauf et al., "Relationship of Effective Molecular Size to Systemic Clearance in Rats of Recombinant Interleukin-2 Chemically Modified with Water-Soluble Polymers"

These articles representing a body of work by a research group describe PEG-rIL-2 preparations that include species with one PEG/rIL-2.

B55 Katre and Knauf, WO 87/00056

This application describes a 1-mer PEGylated ricin A that retained translation inhibition activity approaching free ricin A while 2-mer and higher-mer PEGylated ricin A showed greatly reduced translation inhibition activity. It goes on to state that it may be necessary to PEGylate ricin A to produce only 1-mers.

C74 Koide and Kobayashi, "Modification of Amino Groups in Porcine Pancreatic Elastase with Polyethylene Glycol in Relation to Binding Ability Towards Anti-Serum and to Enzymic Activity"

This article describes modified elastase with one substituted amino group.

C96 Yoshinaga et al., "Effects of Polyethylene Glycol Substitution on Enzyme Activity"

C97 Zalipsky and Lee, "Use of Functionalized Poly(Ethylene Glycol)s for Modification of Polypeptides"

This article, and book chapter that cites to the article, refer to an alkaline phosphatase with PEG substitution at one site.

C79 Kurfurst, "Detection and Molecular Weight Determination of Polyethylene Glycol-Modified Hirudin by Staining after Sodium Dodecyl Sulfate-Polyacrylamide Gel Electrophoresis"

This article describes a PEG-hirudin complex with one PEG attached.

C61 Cunico et al., "Characterization of Polyethylene Glycol Modified Proteins Using Charge-Reversed Capillary Electrophoresis"

This article describes mono-PEG species of a tripeptide and of myoglobin.

C70 Jiang and Dalton, "Chemical Modification of the Hydroxylase of Soluble Methane Monooxygenase Gives One Form of the Protein with Significantly Increased Thermostability and Another That Functions Well in Organic Solvents"

This article describes the covalent modification of hydroxylase with PEG.

C73 Kita et al., "Characterization of a Polyethylene Glycol Conjugate of Recombinant Human Interferon-γ"

This article describes PEG IFN-γ with two PEGs attached, one at the N-terminal amino group and another at either lysine 129 or 131.

C77 Kropachev et al., "Certain Properties of Insulin Modified with Synthetic Polymers"

The article describes polymer-insulin products in which polymer bonding at the lysine ε-amino group was always observed.

C85 Nho et al., "PEG-Modified Hemoglobin as an Oxygen Carrier"

This article describes various PEG-hemoglobin conjugates.

A33 Zalipsky, US 5,324,844
A36 Zalipsky, US 5,612,460
C59 Berger and Pizzo, " Preparation of Polyethylene Glycol-Tissue Plasminogen Activator Adducts That Retain Functional Activity: Characteristics and Behavior in Three Animal Species"
C67 Harris and Wiser, "Characterization of Products Formed From Reaction of Polyethylene Glycol Acetaldehyde with Various Bases"
C68 Jackson et al., "Synthesis, Isolation, and Characterization of Conjugates of Ovalbumin with Monomethoxypolyethylene Glycol Using Cyanuric Chloride as the Coupling Agent"
C86 Nucci et al., "The Therapeutic Value of Poly(ethylene glycol)-Modified Proteins"
C87 Pedder, "Pegylation of Interferon Alfa [sic]: Structural and Pharmacokinetic Properties"
C89 Poznansky and Juliano, "Biological Approaches to the Controlled Delivery of Drugs: A Critical Review"
C90 Smith et al., "Receptor Binding Studies of Polyethylene Glycol (PEG) Modified Granulocyte-Macrophage Colonly Stimulating Factor (GM-CSF) with Dissociated Biological Activites"
C91 Tanaka et al., "Pharmacokinetics of Recombinant Human Granulocyte Colony-Stimulating Factor Conjugated to Polyethylene Glycol in Rats"
C93 Wang et al., "Polyethylene Glycol-Modified Chimeric Toxin Composed of Transforming Growth Factor α and Psuedomonas Exotoxin"
C98 Zimmerman et al., "Schedule Dependency of the Antitumor Activity and Toxicity of Polyethylene Glycol-Modified Interleukin 2 in Murine Tumor Models"

These documents describe conjugates with multiple PEG molecules.

C60 Brygier et al., "Covalent Attachment of Poly(ethyleneglycol) to Peptides and Proteins: Reevaluation of the Synthesis, Properties, and Usefulness of Carbonylimidazol-1-yl-Methoxypoly(ethyleneglycol)

This article states "it is suggested that carbonylimidazol-1-yl-mPEG may be best used to modify α-amino terminal function of proteins selectively."

C69 Jentoft and Dearborn, "Protein Labeling by Reductive Alkylation"

This article states reductive alkylation is a versatile method for derivatizing proteins.

A34 Tam, US 5,589,356

This patent describes methods for the chemical ligation of peptides.

C83 Nathan et al., "Copolymers of Lysine and Polyethylene Glycol: A New Family of Functionalized Drug Carriers"

This article describes copolymers of lysine and polyethylene glycol $(PEG\text{-}Lys)_n$ in which each PEG-Lys has reactive pendent group, the carboxylic acid group of the lysine residues. The reactive pendent groups are stated to be used for derivatization, cross-linking or conjugation with other molecules. Other molecules exemplified are penicillin V and cephradine.

B53 Carmichael et al., EP 567 566 B1
B57 Thompson et al., WO 92/16221
B59 Cox et al., WO 94/12219
B61 Cox et al., WO 95/32003
C58 Benhar et al., "Psuedomonas Exotoxin A Mutants"

These documents describe PEG attachment to proteins through cysteine residues.

Dated: October 25, 2005

Respectfully submitted,

By Greta E. Noland
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Agent for Applicant

Docket No.: 11009/35975C
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Olaf B. Kinstler

Application No.: 09/817,725 Group Art Unit: 1648

Filed: March 26, 2001 Examiner: Not Yet Assigned

For: N-TERMINALLY CHEMICALLY MODIFIED PROTEIN COMPOSITIONS AND METHODS

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT (IDS)

Commissioner for Patents
Washington, DC 20231

Dear Sir:

Pursuant to 37 CFR 1.56, the attention of the Patent and Trademark Office is hereby directed to the references listed on the attached PTO/SB/08. It is respectfully requested that the information be expressly considered during the prosecution of this application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

This Information Disclosure Statement is before the mailing of a first Office Action on the merits so far as is known to the undersigned. No certification or fee is required.

Copies of the patents listed in the attached form PTO/SB/08 are enclosed.

The Commissioner is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper

hereafter filed in this application by this firm) to our Deposit Account No. 13-2855. A duplicate copy of this paper is enclosed.

Dated: March 10, 2003

Respectfully submitted,

By _____

Mark H. Hopkins, Ph.D.
Registration No.: 44,775

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Application No. (if known): 09/817,725 Attorney Docket No.: 11009/35975C

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

on **October 25, 2005** .
Date

Greta E. Noland
Signature

Greta E. Noland
Typed or printed name of person signing Certificate

Note: Each paper must have its own certificate of mailing, or this certificate must identify each submitted paper.

IDS (Citation) by Applicant

PTO/SB/08A (10-01)
Approved for use through 10/31/2002.OMB 0651-0031
U. S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	09/817,725
Filing Date	March 26, 2001
First Named Inventor	Olaf B. Kinstler et al.
Art Unit	1648
Examiner Name	Not Yet Assigned
Attorney Docket Number	11009/35975C

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	A30	6,027,720	02-22-2000	Kuga *et al.*	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	B46	GB 2 193 631	02-17-1988			
	B47	EP 0 340 741	11-08-1989			

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant

PTO/SB/08a/b (08-03)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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FOURTH INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet	1	of	4

Complete if Known	
Application Number	09/817,725
Filing Date	March 26, 2001
First Named Inventor	Kinstler *et al.*
Art Unit	1654
Examiner Name	Billy Dell Chism
Attorney Docket Number	11009/35975C

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number: Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	A31	3,772,264	11-13-1973	Bayer *et al.*	
	A32	5,109,120	04-28-1992	Ueno and Fujino	
	A33	5,324,844	06-28-1994	Zalipsky	
	A34	5,589,356	12-31-1996	Tam	
	A35	5,597,797	01-28-1997	Clark	
	A36	5,612,460	03-18-1997	Zalipsky	
	A37	5,646,113	07-08-1997	Attie *et al.*	
	A38	5,661,122	08-26-1997	Clark *et al.*	
	A39	5,747,646	05-05-1998	Hakimi *et al.*	
	A40	5,935,924	10-10-1999	Bunting *et al.*	
	A41	6,673,347	01-06-2004	Offord *et al.*	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document: Country Code[3]-Number[4]-Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	B31	JP-62-115280 (equivalent of B20)	05-26-1987	Takeda Chemical Industries Ltd.		
	B32	JP-62-129298 (English language translation included)	06-11-1987	Chugai Pharmaceutical Co. Ltd.		
	B33	JP-62-236488 (English language translation included)	10-16-1987	Chugai Pharmaceutical Co. Ltd.		
	B34	JP-62-236497 (English language translation included)	10-16-1987	Chugai Pharmaceutical Co. Ltd.		
	B35	JP-62-289522 (equivalent of B23)	12-16-1987	Cetus Corp.		
	B36	JP-62-503171 (equivalent of B49)	12-17-1987	Cetus Corp.		
	B37	JP-63-10800 (equivalent of A32)	01-18-1988	Takeda Chemical Industries Ltd.		
	B38	JP-63-126900 (English language translation included)	05-30-1988	Takeda Chemical Industries Ltd.		
	B39	JP-63-500636 (English language translation included)	03-10-1988	Kirin Amgen Inc. (US)		
	B40	JP-63-60938 (English language translation included)	03-17-1988	Meiji Milk Prod. Co. Ltd.		
	B48	DE 29 30 542 (English language translation included)	02-12-1981	Hoechst AG.		
	B49	EP 229 108	07-22-1987	Cetus Corp.		
	B50	EP 402 378B	12-19-1990	Cetus Oncology Corp.		
	B51	EP 426 488 B	05-08-1991	Nihon Chemical Research Kabushiki Kaisha also known as JCR Pharmaceuticals Co., Ltd.		
	B52	EP 510 356A	10-28-1992	F. Hoffmann-La Roche AG		
	B53	EP 567 566 A	11-03-1993	Amgen Inc.		

Examiner Signature		Date Considered	

PTO/SB/08a/b (08-03)
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(Use as many sheets as necessary)

Sheet 2 of 4

Complete if Known	
Application Number	09/817,725
Filing Date	March 26, 2001
First Named Inventor	Kinstler *et al.*
Art Unit	1654
Examiner Name	Billy Dell Chism
Attorney Docket Number	11009/35975C

	B54	JP-5-170796 (English language translation included)	07-09-1993	Sumitomo Pharmaceuticals Company Limited		
	B55	WO 87/00056 (PCT)	01-15-1987	Cetus Corp.		
	B56	WO 90/05534 (PCT)	05-31-1990	Genentech, Inc.		
	B57	WO 92/16221 (PCT)	10-01-1992	Synergen, Inc.		
	B58	WO 93/00109 (PCT)	01-07-1993	Genentech, Inc.		
	B59	WO 94/12219 (PCT)	06-04-1994	Synergen, Inc.		
	B60	WO 95/00846 (PCT)	01-05-1995	TAM, James P.		
	B61	WO 95/32003 (PCT)	11-30-1995	Amgen Boulder Inc.		

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	C24	CRC Standard Mathematical Tables, 26th ed., (Beyer, W.H., Ed.) CRC Press, Inc. Boca Raton, FL, 1981, p. 125	
	C26	FILGRASTIM Clinical Practice, Morstyn, G. and T.M. Dexter, Eds., Marcel Dekker Inc., New York, NY (1993), p.351	
	C55	ACHARYA *et al.*, *J. Biol. Chem.*, "Schiff Base Adducts of Glyceraldehyde with Hemoglobin", 258(4): 2296-2302 (1983)	
	C56	ACHARYA *et al.*, *J. Biol. Chem.*, "Reductive Hydroxyethylation of Hemoglobin A", 258(22): 13761-13767 (1983)	
	C57	ACHARYA *et al.*, *J. Biol. Chem.*, "Selectively in the Modification of the α-Amino Groups of Hemoglobin on Reductive Alkylation with Aliphatic Carbonyl Compounds", 260(10): 6039-6046 (1985)	
	C58	BENHAR *et al.*, *J. Biol. Chem.*, "*Pseudomonas* Exotoxin A Mutants: Replacement of Surface-Exposed Residues in Domain III with Cysteine Residues that can be Modified with Polyethylene Glycol in a Site-Specific Manner", 269(18):13398-13404 (1984) Issue of May 6 Received 8/26/93	
	C59	BERGER and PIZZO, *Blood*, "Preparation of Polyethylene Glycol-Tissue Plasminogen Activator Adducts that Retain Functional Activity: Characteristics and Behavior in Three Animal Species", 71(6)(June):1641-1647 (1988)	
	C60	BRYGIER *et al.*, *Applied Biochemistry and Biotechnology*, "Covalent Attachment of Poly(ethyleneglycol) of Peptides and Proteins", 42:127-135 (1993)	
	C61	CUNICO *et al.*, *J. Chromatography*, "Characterization of polyethylene glycol modified proteins using charge-reversed capillary electrophoresis", 559:467-477 (1991)	
	C62	DAS *et al.*, *J. Amer. Chem. Soc.*, "New model visual pigments. Spectroscopy of Poly(ethylene glycol) Peptide Schiff Bases of Retinal", 101(1):239-240 (1979)	
	C63	DELGADO *et al.*, *J. Biochem. Biophys. Methods*, "Quantitative analysis of polyethylene glycol (PEG) in PEG-modified proteins/cytokines by aqueous two-phase systems", 29:237-250 (1994)	
	C64	DIDONATO *et al.*, *J. Biol. Chem.*, "Selective Carboxymethylation of the α-Amino Groups of Hemoglobin", 258(19): 11890-11895 (1983)	

Examiner Signature		Date Considered	

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Sheet 3 of 4

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Filing Date	March 26, 2001
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Art Unit	1654
Examiner Name	Billy Dell Chism
Attorney Docket Number	11009/35975C

	C65	EHRAT and LUISi, *Biopolymers*, "Synthesis and Spectroscopic Characterization of Insulin Derivatives Containing One or Two Poly(ethylene oxide) Chains at Specific Positions", 22:569-573 (1983)	
	C66	FRANCIS *et al., Biomedicine and Pharmacotherapy*, "PEG-Cytokines: Improved Pharmaceutical Properties and Dissociation of Individual Bioactivities", 46(5-7):305 (Abstract 133) (1992)	
	C67	HARRIS and WISER, American Chemical Society, "Characterization of products formed from reaction of polyethylene glycol acetaldehyde with various bases", 201st National Meeting, Atlanta, GA, April 14-19, 1991, Abstracts Part 2, Abstract 78	
	C68	JACKSON *et al., Anal. Biochem.*, "Synthesis, Isolation, and Characterization of Conjugates of Ovalbumin with Monomethoxypolyethylene Glycol Using Cyanuric Chloride as the Coupling Agent", 165:114-127 (1987)	
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	C70	JIANG and DALTON, *Biochimica et Biophysica Acta*, "Chemical modification of the hydroxylase of soluble methane monooxygenase gives one form of the protein with significantly increased thermostability and another that functions well in organic solvents", 1201:76-84 (1994)	
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FOURTH INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet	4	of	4

Complete if Known	
Application Number	09/817,725
Filing Date	March 26, 2001
First Named Inventor	Kinstler *et al.*
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